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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,228	09/29/2003	Samir M. Hanash	31755-A-PCT-USA-I	1891

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,228	HANASH ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 2, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2006 has been entered for Application No.10/674,228.

2. An action on the RCE follows.

3. Claims 1-4 are pending and are currently under consideration.

Specification Objection

4. The abstract of the disclosure is objected to because the abstract contains too many words. Correction is required. See MPEP § 608.01(b).

5. The disclosure is objected to because of the following informalities:
The identifying data of all prior applications for which benefits are claimed should be provided in either the first sentence(s) of the specification or in an application data sheet. See MPEP § 202.02

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1 wherein the sample of cells is derived from the subject's tumor does not reasonably provide enablement for the method of claim 1 wherein the sample of cells is derived from a continuous cell line representative of the subject's tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claim is drawn to the method of claim 1 wherein the sample of cells is derived from a continuous cell line representative of the subject's tumor.

Given that the specification as originally filed does not define the term "representative of" it will be assumed for examination purposes that the claim is drawn to cell lines with the same characteristic as the tumor of the patient. This means that the cell line must be representative of, i.e. have the same characteristics as, the subject's tumor cells.

The specification teaches that the source of cells for identifying proteins to which a subject with cancer produces autoantibodies can be from cultured cell lines, in addition to other sources, p. 3, lines 27-29. The specification further teaches that protein spots corresponding to proteins that have elicited specific autoantibodies are distinguishable from nonspecific spots based on their presence in Western Blots prepared with patients' sera compared to control sera, and/or the presence of a spot in the disease tissues or cell lines or extracts compared to control tissues, cell lines or extracts, p. 10, lines 23-38. Specifically, the specification teaches that the neuroblastoma cell line SY5Y was used as a protein source for the claimed method, p. 15, lines 16-17.

The specification further teaches that sera were obtained from patients with neuroblastoma as well as from patients with other tumor types including cancer of the lung, esophagus, sarcomas and Wilms tumors, p. 15, lines 13-15. Further the specification teaches that several immunoreactive spots occurred in Western blots of neuroblastoma patient sera. These spots were absent in Western blots of other tumors or in Western blots of neuroblastoma tumors that were treated with control sera, p. 16, lines 8-10.

One cannot extrapolate the teaching of the specification to the scope of the claims because one of skill in the art could not predict that the method would function as claimed because the teaching of specification that cell lines are used for a protein source for the method, specifically the SY5Y neuroblastoma cell line, is not sufficient to establish that the sample of cells is derived from a continuous cell line **representative** of the subject's tumor. In particular, characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish

cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that

new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Since the art makes it clear that cell lines are not representative of *in vivo* cancer cells, that is they do not have the same characteristics as *in vivo* cancer cells, no one of skill in the art would believe it more likely than not that the claimed invention would function as claimed, that is the method of claim1 wherein the sample of cells is derived from a continuous cell line representative of the subject's tumor.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitations of a method for identifying proteins, to which a subject with cancer produces autoantibodies, said method **consisting essentially of** (emphasis added): (a) extracting proteins from a sample of cells; (b) separating the extracted proteins by two-dimensional electrophoresis; (c) transferring the proteins separated by two-dimensional electrophoresis to a membrane; (d) incubating the membrane with antiserum from a subject known to have the cancer; (e) detecting the proteins to which autoantibodies in the patients serum have bound; and (f) comparing the proteins to which antibodies in the subject's serum sample bind to proteins to which antibodies in control serum sample bind, wherein those proteins bound by antibodies in the subject's serum but not the control serum are identified as proteins to which a subject with cancer produces autoantibodies.

Claim 1 has no clear support in the specification and the claims as originally filed. In particular, examiner's review revealed that there is nothing in the specification to support a method for identifying proteins, to which a subject with cancer produces autoantibodies consisting essentially of the aforementioned steps. The subject matter claimed in claim 1 alters the scope of the invention as originally disclosed in the specification.

If applicant should disagree with this rejection, applicant should submit evidence pointing to the serial number, page and line where support can be found for the disputed terminology.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirsch et al., IDS filed on 0711 112005, J Cancer Res Clin Oncol. 1988; 114 (2): 204-7.

It is noted for applicant's convenience that the phrase "consisting essentially of" for purposes of art is interpreted to mean comprising. In particular, MPEP, 2111.03 defines the phrase "consisting essentially of" as limiting the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics

actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355.

Additionally, given that the instant specification teaches that an object of the present invention is to provide a procedure for the identification of cellular protein antigens and for the detection of antibodies to specific cellular protein antigens in the serum of patients with cancer and the prior art reference also teaches a method for the identification of cellular protein antigens and for the detection of antibodies to specific cellular protein antigens in the serum of patients with cancer and there is no clear indication in the specification or claims of what the basic method characteristics consist essentially of, it is clear that the addition of the initial screening with one-dimensional gel electrophoresis does not materially affect the basic and novel characteristics of the claimed invention. Thus, for examination purposes, the phrase "consisting essentially of" is interpreted to mean comprising.

Claims 1-4 are drawn to a method of identifying proteins that induces autoantibodies in cancer patients, consisting essentially of isolating proteins from cancer cells, more specifically cells derived from the subject's tumor (claim 2), or from a continuous cell line representative of the subject's tumor (claim 3), followed by subjecting isolated proteins to two-dimensional PAGE, followed by Western blot analysis with sera from cancer patients as compared to sera from normal control patients, wherein the proteins bound by antibodies present in the cancer patients serum but not the normal control serum are identified as proteins to which a subject with cancer produces autoantibodies. Since the specification does not defined the limitation "derived from the subject's tumor" in claim 2 and "derived from a continuous cell line representative of the subject's tumor" in claim 3, the limitations are broadly interpreted as the cells that are being

used to isolate the proteins being subjected to two dimensional analysis are from the same type of cancer cells as the patient who provides the serum containing autoantibodies.

Hirsch et al., teach a method of identifying proteins that induces autoantibodies in Hodgkin's disease which is a form of cancer, i.e. lymphoma, comprising the steps of isolating proteins from L428 cancer cells derived from Hodgkin's disease cancer patients, followed by subjecting isolated proteins to two-dimensional PAGE, followed by Western blot analysis with sera from cancer patients as compared to sera from normal control patients, wherein the proteins bound by antibodies present in the cancer patients serum but not the normal control serum are identified as proteins to which a subject with cancer produces autoantibodies. Note page 204 under the heading Materials and methods for the gel-electrophoresis, and Western blot, and the picture of the identified proteins in the two-dimensional gel at Fig. 1A, 2, and 3. Schaadt et al., Int J Cancer. 1980 Dec 15, 26(6): 723-31 was previously provided in the office action mailed August 18, 2005 to present evidence that L428 used in Hirsch et al., are cells derived from the subject's tumor and from a continuous cell line representative of the subject's tumor. In other words, the cells being used are derived from Hodgkin's disease.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

To the extent the prior art does not specifically not teach the method of claim 1, Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirsch et al. (J Cancer Res Clin Oncol. 1988, 114 (2): 204-7 IDS) and further in view of Krska et al. (J. Bacteriology, 1993, 175 (20): 6433-6440).

The claims are drawn to a method for identifying proteins, to which a subject with cancer produces autoantibodies, said method consisting essentially of: (a) extracting proteins from a sample of cells; (b) separating the extracted proteins by two-dimensional electrophoresis; (c) transferring the proteins separated by two-dimensional electrophoresis to a membrane; (d) incubating the membrane with antiserum from a subject known to have the cancer; (e) detecting the proteins to which autoantibodies in the patients serum have bound; and (f) comparing the proteins to which antibodies in the subject's serum sample bind to proteins to which antibodies in control serum sample bind, wherein those proteins bound by antibodies in the subject's serum but not the control serum are identified as proteins to which a subject with cancer produces autoantibodies (claim 1); the method of claim1 wherein the sample of cells is derived from the subject's tumor (claim 2); the method of claim1 wherein the sample of cells is derived form a continuous cell line representative of the subject's tumor (claim 3); the method of claim 1 wherein the step of detecting the proteins to which autoantibodies in the subject's serum sample have bound comprises the use of a signal-generating component bound to an antibody that is specific for antibodies in the subject's sample (claim 4).

Hirsch et al. teach as set forth above, but do not specifically teach said method consisting essentially of: (a) extracting proteins from a sample of cells; (b) separating the extracted proteins by two-dimensional electrophoresis; (c) transferring the proteins separated by two-dimensional electrophoresis to a membrane; (d) incubating the membrane with antiserum from a subject known to have the cancer; (e) detecting the proteins to which autoantibodies in the patients serum have bound; and (f) comparing the proteins to which antibodies in the subject's serum sample bind to proteins to which antibodies in control serum sample bind, wherein those proteins

bound by antibodies in the subject's serum but not the control serum are identified as proteins to which a subject with cancer produces autoantibodies .

Krska et al. (p. 6435, left column) teach a method conventional in the art at the time of the invention consisting of identifying proteins by extracting proteins from a sample of cells; separating the extracted proteins by two-dimensional electrophoresis; transferring the proteins separated by two-dimensional electrophoresis to a membrane; and using a signal generating component bound to an antibody that is specific for proteins in the sample.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify proteins by resolving the proteins with two-dimensional electrophoresis and performing a Western blot using the method of Hirsch et al. or the method of Krska et al. because both of the methods were conventionally used in the art at the time of the invention. Since the methods were conventionally known at the time of the invention one would have had a reasonable expectation of success of using either or both of the method of Hirsch et al. or the method of Krska et al. to identify proteins to which a subject with cancer produces autoantibodies.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

SUSAN UNGAR, PH.D
PRIMARY EXAMINER